The Examiner has withdrawn claims 1-6 and 8-30 from consideration. In the Office Action, the Examiner explained that claims 8-11 all require the evaluation of non-elected mutations, such as 101P, etc. and are therefore withdrawn from examination at this time as being directed to non-elected mutations subject matter. The Examiner goes on to state that the mutation election is a species election and that future examination of the other mutation election will occur if the elected species correspond to allowable subject matter. The Applicants, however, respectfully point out that claim 8 recites a method according to claim 7, wherein said at least one mutation of said first nucleic acid is 103S, which is an elected species. Thus, even though claim 8 contains the additional limitation of at least one additional mutation 101P, if the species 103S of claim 7 is patentable over the prior art, claim 8 is also patentable over the prior art. No evaluation of further species of claim 7 is necessary. This is in contrast to claim 9, which is directed to a method of claim 7 wherein said at least one mutation of said first nucleic acid is chosen from 44D, 44A and 118I, thus requiring evaluation of non-elected mutations 44D and 44A of claim 7. Therefore, Applicants respectfully request that claim 8 be reconsidered.

Objections

The disclosure was objected to because of the following informalities:

page 24, table 2b, there was an unclear abbreviation of Pi; and

page 6 contained two hyperlinks.

Applicants have amended the specification to correct these informalities. No new matter was introduced. Applicants respectfully request that these objections be withdrawn.

Rejection under § 112, first paragraph

Claim 7 was rejected under 35 USC § 112, first paragraph, because according the Examiner, while the specification is enabling for a method of evaluating the effectiveness of antiretroviral therapy of an HIV-infevted patient with the 118I mutation, it does not reasonably provide enablement for the correlation of resistance regarding mutation 103S and 88T. Applicants respectfully traverse.

Applicants understand the Examiner's position as claim 7 would require undue experimentation to practice and thus lacks enablement. The Examiner's support for this contention is that while step (ii) of claim 7 includes mutations (a) 103(s), (b) 118I, and (c) 88T, table 5, page 35 of the instant specification only reports the frequency of ZDV and 3TC resistance-correlated mutation, 118I. According to the Examiner, the instant specification only contains allegations of resistance correlations for mutations 103S and 88T without supporting evidence. See, page 4, Official Actions of December 4, 2001.

Applicants disagree with the Examiner's contention that the instant specification only contains allegations of resistance correlations for mutations 103S and 88T. The Applicants are not "alleging" that there is a resistance correlation for mutations 103S and 88T. On the contrary, the Applicants are **reporting** that they have discovered that there is a resistance correlation for mutations 103S and 88T and all of the mutations

recited in claim 7. The Applicants actually determined through experimental procedures that there is a resistance correlation for all of the mutations recited in claim 7.

More specifically, the instant specification describes that a combinational approach, as described in the examples, involving genotypic and phenotypic resistance testing was used to correlate mutations with resistance phenotypes. Specification, p. 14-20. The specification also explains that for many mutations reported and claimed, in addition to the observation of the genotypic and phenotypic profiles in isolates from clinical practice, site-directed mutants were generated to confirm that these mutations actually form the basis of this pattern of drug resistance. The results of these evaluations are reported, for example, in Table 2a and 2b.

The Applicants do not see the need to provide the raw data for every mutation determined. Examples 1 and 2 give a specific details regarding the above described experiments for several mutations, including 118I, as pointed to by the Examiner. This along with the description described above regarding how a mutation correlation was determined is enough to enable the pending claims for all of the mutations recited. Since the Examiner admits on the record that the specification is enabled for a method of evaluating the effectiveness of antiretroviral therapy of an HIV-infected patient with the 118I mutation, the only way for the Examiner to contend that claim 7 also isn't enabled for all other mutations recited is for the Examiner to doubt the Applicants statements regarding the determination of mutations, including the determination of 103S and 88T. Without a reason to doubt the truth of the statements made in the patent application, the application must be considered enabling. See, e.g., 35 U.S.C. § 112 First Paragraph Enablement Training Manual, p.5.; In re Wright, 99 F.2d 1557,

1562(Fed Cir. 1993); and In re Marzocchi, 439 F. 2d 220 (CCPA 1971). Applicants therefore respectfully request that the rejection be withdrawn.

Rejections under § 112, second paragraph

Claim 7 was rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7, lines 14 and 15 was rejected in regard to "mutation chosen from 88T and combination of mutations 33F and 90M" as vague and indefinite. Applicants respectfully traverse. However, in an effort to expedite prosecution, Applicants have amended claim 7 to clarify the claim language and remove the language rejected by the Examiner. Applicants request that this rejection be withdrawn.

Claim 7 was rejected as containing abbreviations such as NNRTI, NRTI and PI which cause the claim to be vague and indefinite. Applicants respectfully traverse. However, in an effort to expedite prosecution, Applicants have amended claim 7 to insert the full names. Applicants request that this rejection be withdrawn.

Finally, Claim 7 was rejected as containing unclear designations 103S, 118I and 88T. The Examiner seems to suggest that the correct designation should be K103S, V188I, and N88T. Applicants respectfully traverse. As the Examiner is aware, the designation K103S refers to the mutation of amino acid K at position 103 to amino acid S. Similarly, the designation 103S, refers to the mutation of position 103 to amino acid S regardless of the original amino acid, *i.e.*, K103S, V103S, or T103S. What is important in conferring resistance is the existence of S at 103 not what was the

predecessor amino acid. Thus Applicants contend that 103S more clearly defines their invention. The primary purpose of the requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. M.P.E.P. § 2173. If the scope of the invention sought to be patented can be determined from the language of the claims with a reasonable degree of certainty, then a rejection under 35 U.S.C. § 112, second paragraph, is not appropriate. See In re Wiggins, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973). There is no doubt as to the certainty of the designation 103S, etc. Thus, Applicants request that this rejection be withdrawn.

Rejections under § 103(a)

Claim 7 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Jon. H. Condra et al (Journal of Virology, Dec. 1996) and Petropoulos et al. (WO 99/67427, 29 Dec. 1999). Applicants respectfully traverse.

The Examiner's position is understood as follows. It would have been obvious to one of ordinary skill in the art at the time of the instant invention to carry out the method of claim 7 because all of the steps therein are either described or suggested in the above references. Step (i) of claim 7 is on page 73, line 4-5 of Petropoulos et al. Step(ii) of claim 7 is taught on page 8270, 2nd column and page 8272, table 1 of Condra et al, which motivates and suggests the correlation between N88T with a drug resistace. Step (iii) of claim 7 is also in Condra et al. in table 1, which shows that in the presence of N88T the effectiveness of a therapy was evaluated.

To establish a *prima facie* case of obviousness, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. See M.P.E.P. § 2143. Furthermore, the teaching or suggestion to make the claimed combination must be found in the prior art, not in Applicants' disclosure. See *In re Vaeck*, 947 F.2d 488, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). While the Examiner argues that the generic listing of mutation resistance in Table 1 is "deemed" to motivate and suggest that mutant N88T correlates with drug resistance, he has provided no evidence to his statement.

Table 1 of Condra is exactly what the Examiner describes it to be: "a generic listing." More specifically, table 1 merely lists all the mutations that were present in a patient isolate sample and the relationship of that sample to resistance of indinavir. The Example relied on by the Examiner, patient O, shows an isolate with 8 mutations in the protease sequence, one of which was N88T. There is, however, no teaching or suggestion of which of the 8 mutations or combination of mutations may be responsible for the observed resistance. From the teaching of the reference, it is just as logical to assume that the observed resistance was due to the presence of all 8 mutations as compared to the N88T mutation. Thus, there is no suggestion or motivation to choose N88T as responsible for resistance nor has the Examiner provided one. The Examiner can not rely on his conclusory statement deeming that Table 1 motivates and suggests mutant N88T correlates with drug resistance. As recently reiterated by the Federal Circuit, one "cannot rely on conclusory statements when dealing with particular combinations of prior art and specific claims, but must set forth the rationale on which it

relies." In re Sang-Su Lee, No. 00-1158, at 11 (Fed Cir. January 18, 2002). Thus, Applicants contend the Examiner has failed to establish a *prima facie* case of obviousness and Applicants respectfully request that this rejection be withdrawn.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: March 1, 2002

By: _____
Anthony C. Tridico
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APPENDIX TO RESPONSE AND AMENDMENT

IN THE SPECIFICATION

Amendments to 2nd full paragraph of Page 6:

"Extensive genetic analysis of resistant viral isolates generated through *in vivo* or *in vitro* selection has revealed that resistance is generally caused by mutations altering the nucleotide sequence at some specific site(s) of the viral genome. The mutational patterns that have been observed and reported for HIV-1 and that are correlated with drug resistance are very diverse: some antiretroviral agents require only one single genetic change, while others require multiple mutations for resistance to appear. A summary of mutations in the HIV genome correlated with drug resistance has been compiled. See Schinazi, R.F., Larder, B.A. & Meliors, J.W. 1997. Int. Antiviral News. 5, 129-142 (1997). Additionally, an electronic listing with mutations has also become available **on the internet at sites such as hiv-web.lanl.gov or www.viralresistance.com** [at http://hiv-web.lanl.gov or http://www.viralresistance.com]."

Amendments to Table 2b on Page 24:

Table 2b: Novel Protease Mutations and the Correlated Drug Resistance

Protease Mutation	Resistant to:
33F + 90M	PI
88T	**[PI] PI**

IN THE CLAIMS

7. (Amended) A method of evaluating the effectiveness of an antiviral therapy of an HIV-infected patient comprising:

(i) collecting a sample from an HIV-infected patient;

(ii) determining whether the sample comprises at least one nucleic acid chosen from:

(a) a first nucleic acid encoding HIV reverse transcriptase [having] **comprising at least one mutation chosen from:**

1) at least one mutation chosen from 88E, 101H, 101N, 101P, 101Q, 101T, 103H, 103S, 179I, 179E, 181V, 190E, 190S, **and** 190T,

2) [and the combination of] mutations 103 R and 179D, **or**

3) combinations of 1) and 2),

in which the presence of said at least one mutation correlates with resistance to at least one **Non-Nucleoside Reverse Transcriptase Inhibitor** (NNRTI);

(b) a second nucleic acid encoding HIV reverse transcriptase [having] **comprising** at least one mutation chosen from 69S-[S-S], 184G, 184L, 215 V, 44D, 44A, and 118I,

in which the presence of said at least one mutation correlates with resistance to at least one **Nucleoside Reverse Transcriptase Inhibitor** (NRTI); and

(c) a third nucleic acid encoding HIV protease [having] **comprising** at least one mutation chosen from:

1) 88T,

2) [and the combination of] mutations 33F and 90M, **or**

3) combinations of 1) and 2),

in which the presence of said at least one mutation correlates with resistance to at least one **Protease Inhibitor** (PI); and

(iii) using the presence of said at least one nucleic acid to evaluate the effectiveness of said antiviral therapy.